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EXAMINER	
YU, MISOOK	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 12/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/028,384	PERREAULT ET AL.	
	Examiner	Art Unit	
	MISOOK YU, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *08 October 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-83* is/are pending in the application.

4a) Of the above claim(s) *18-47,53-67,70-77 and 80* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-17,48-52,68,69 and 78, 79, 81-83* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12/20/01, 07/08/02*. 11/04/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *See Continuation Sheet*.

Continuation of Attachment(s) 6). Other: Notice to comply sequence rules, and Exhibit A (sequence alginment).

DETAILED ACTION

Election/Restrictions

Applicant's election with traverse of group I in the reply filed on 10/08/2004 is acknowledged. The traversal is on the ground(s) that unity of invention exist each groups, especially groups I and II. This is not found persuasive because unity of invention does not apply to the instant application because the application is not a 371.

The requirement is still deemed proper and is therefore made FINAL.

Claims 18-47, 53-67, 70-77, and 80 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention, there being no allowable generic or linking claim.

Claims 1-83 are pending. Claims 1-17, 48-52, 68, 69, 78, 79, 81-83 are examined on merits.

Sequence Rules

This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 CFR 1.821(a)(1) and (a)(2).The specification is objected to because of the following informalities: the numerous peptide sequences in Fig. 1, and Table 1 at pages 16-22, pages 47-49, and the two primers at page 44 all needs SEQ ID NOs.

However, this application fails to comply with the requirements of 37 CFR 1.821 through 1.825 for the reason(s) set forth below or on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures. 37 CFR 1.821(a) presents a definition for

"nucleotide and/or amino acid sequences." Nucleotide and/or amino acid sequences as used in 37 CFR 1.821 through 1.825 are interpreted to mean an unbranched sequence of four or more amino acids or an unbranched sequence of ten or more nucleotides. Branched sequences are specifically excluded from this definition. Sequences with fewer than four specifically defined nucleotides or amino acids are specifically excluded from this section. "Specifically defined" means those amino acids other than "Xaa" and those nucleotide bases other than "n" defined in accordance with the World Intellectual Property Organization (WIPO) Handbook on Industrial Property Information and Documentation, Standard ST.25: Standard for the Presentation of Nucleotide and Amino Acid Sequence Listings in Patent Applications (1998), including Tables 1 through 6 in Appendix 2 (see MPEP § 2422). Note attached "Notice to Comply with requirement for patent application containing nucleotide sequence and/or amino acid sequence disclosures".

Specification

The disclosure is objected to because it (note page 16) contains an embedded hyperlink and/or other form of browser-executable code. Applicant is required to delete the embedded hyperlink and/or other form of browser-executable code. See MPEP § 608.01.

Claim Objections

Claims 6, 8, and 11 are objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. In order to be a proper dependent claims, each and every species of the subgenus

encompassed by the property boundary drawn by the dependent claims should belong to the genus of the base claim that the dependant claims depend on. The base claim 1 says the claimed genus should be a human nucleic acid. However, at least one species encompassed by the dependent claims 6, 8, and 11 does not belong to a human nucleic acid. Note the nucleic acid encoding the amino acid sequence having 100 % amino acid sequence identity to SEQ ID NO:8, which belong the property boundary drawn by Claims 6, 8, and 11, does not belong to the property boundary drawn by claim1. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form.

Claim 49 is objected to because of the following informalities: SIMP' appears to be a typographical error. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 14, 48, 50, and 69 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 14, 48, 50, and 69 recite "under high stringency conditions" but it is not clear what the metes and bounds are. The specification does not define the limitation. Since what will hybridize would depend on hybridization specific conditions, the property boundary drawn by "under high stringency conditions" is vague and unclear.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, 48-52, 68, 69, 78, 79, and 81-83 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for nucleic acid molecules encoding the three peptides shown in Fig. 1 in vitro use, does not reasonably provide enablement for any other nucleic molecules. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors considered when determining if the disclosure satisfies the enablement requirement and whether any necessary experimentation is "undue" include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re Wands*, 858 F.2d.

Based on the specification that the new discovery disclosed in the instant application is SEQ ID NO:1 encoding a human protein, this scope of enablement rejection is made based on the interpretation of claims 1-17, 48-52, 68, 69, 78, 79, 81-83 as drawn to an isolated nucleic acid molecules encoding peptides binding to an HLA antigen and is recognized by cytotoxic T lymphocytes for use in antisense therapy

and/or a pharmaceutical. Further, claim 79 is broadly interpreted to encompass transfromed cells, which are not isolated and are comprised within an organism.

Riott et al (Immunology, Fourth Edition, 1996, Mosby, page 7.9-7.11) teach that a foreign protein is entered in a host due to infection or other event such as cancer development in a host, it is broken down into short chains of amino acids known as peptides. The cell then "presents" these cleaved peptides on its surface via a protein known as MHC, which stands for major histocompatibility complex. In this manner, the cell "marks" itself to be destroyed. Special immune system cells known as cytotoxic T lymphocytes (CTLs) then recognize and destroy the marked cells. CTLs are antigen-specific; that is, the introduction of a particular antigen into the body activates specialized CTLs that recognize that antigen. The CTLs then target those cells whose surfaces are marked with a fragment of the activating antigen. T cells recognizes cell-bound antigen in association with MHC molecules. MHC class I and class II act as guidance systems for T cells. This is known as MHC restriction. Only a minority of peptide fragments from a protein antigen is able to bind particular MHC molecules. Different MHC molecules bind different sets of peptides. Riott et al specifically teach Fig. 7.22 and Fig. 7.23, and also page 7.10, right column that the peptides sizes 12-15 are optimal for MHC molecule class I and certain amino acids at certain positions are critical for binding to MHC class I.

The specification does not establish the biological function of the newly discovered protein, other than disclosing the three peptides (as shown in Fig. 1) fragments from instant SEQ ID NO:2 encoded by SEQ ID NO:1 work as T cell epitopes.

The specification does not disclose common structural attributes that stimulate an immune response and binds to one or more MHC molecules presented on the surface of cells. There is insufficient guidance regarding the parameters and sequence of peptides which correlate with the ability to stimulate T cell with any MHC molecule and generate CTLs with claimed specifity/activity. There is insufficient guidance regarding selection of peptides that meet the instant criteria of stimulating T lymphocytes with specific activity. Thus, there is insufficient guidance regarding the parameters and sequences of peptides which correlate with the ability to be recognized by the specific CTL clone.

US Pat. 5,840,839 (Nov. 24, 1998) teach at column 19 that finding a peptide that binds to a MHC molecules and stimulates immune response is not a trivial matter. The '839 patent at column 19, lines 53 to 67 teaches that structure a T cell epitope that stimulates immune response in context of MHC molecules is unpredictable in the current state of art. The '839 patent at columns 19-20, and Table 1 teaches that the various candidate T cell epitopes selected based on theoretical binding motif of one class of MHC molecule, i.e. HLA-A31 do not work when they are experimentally tested as shown in Table 1. This suggests that theoretically selected T cell binding motifs have to be tested experimentally in order to determine whether they are actually T cell epitopes or not.

The specification provides insufficient guidance with regard to theses issues and provides no working examples of a peptide that would work with any MHC molecule. Considering the state of art, the broad scope of claims in respect to the nature of

peptide and also to the nature of MHC molecules, it is concluded that that undue experimentation is required to practice the claimed invention. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Searching potential T-cell epitopes in instant SEQ ID NO:2 using existing software (this use is considered as research, not patentable use) does not require undue experimentation. Undue experimentation is required to use the potential T-cell epitopes as immunogen to illicit anti-tumor response i.e. using as an tumor antigen peptide in a subject. The specification fails to teach how administration of the claimed peptide would produce a sufficient amount of CTLs, to destroy tumor cells expressing SEQ ID NO:2. Cancer therapy using immunogen is still unpredictable in the art. The specification teaches that SEQ ID NO:2 is a self antigen (note the claim construction of 1-3, and 6 for example), rather than a mutated antigen, as it is expressed on normal tissues as well as cancerous tissues and that self-tolerance may eliminate T cells that are capable of recognizing these epitopes with high avidity (Sherman, LA et al, 1998, Critical reviews in Immunol, 18(1-2): 47-54, see especially at the abstract and Table 2). In other words, only CTLs with low affinity are left, which may not be optimal for tumor elimination *in vivo*. One of the problem is that after some period of time in the presence of tumor cells, T cells may lose their functional activity. Lauritzsen et al (International Journal of Cancer, 1998, Vol. 78, pp. 216-222) teach that a clonal deletion of thymocytes is a major event in T-cell tolerance which could lead to a tumor escape mechanism. In transgenic mice homozygous for HLA-specific CD+4 T-cells which are

specific for a MOPC315 plasmacytoma, injection of a large number of tumor cells results in apoptosis of immature and mature transgenic CD+4+8 and CD+4 thymocytes. This negative selection was specific for the transgenic thymocytes that would complement the idiotype of the immunoglobulins of the MOPC315 plasmacytoma, because injection of tumor cells from a plasmacytoma which had a different idiotype of immunoglobulins failed to elicit the clonal deletion. Lauritzsen et al teach that injection of purified MOPC315 protein, versus the tumor cells, caused a profound reduction of the specific thymocytes specific to the idiotype of the plasmacytoma. Lauritzsen et al conclude that deletion of tumor specific thymocytes may represent a major escape mechanism in patients with cancers that secrete of shed antigens. In the instant case, the antigens are known self-antigens. It would be reasonable to conclude that said normal antigens are presented within the thymus to developing thymocytes and T-cells with high affinity for said antigens are deleted as "self". It would be also reasonable to conclude that administration of the claimed polypeptides or cells expressing said polypeptides would not result in an efficacious vaccine as a T-cell response would not be evoked due to the process of clonal deletion in the thymus, rendering the host devoid of T-cells which are specific to the self-protein. Sarma et al (Journal of Experimental Medicine, 1999, Vol. 189, pp. 811-820) states that a critical issue in therapeutic regiments comprising the administration of tumor antigens for immunotherapy is whether unmutated tumor antigens which are expressed in normal cells impose special restrictions on the CTL response in vivo. Using transgenic mice wherein the antigen specific T cells specific for the P1A non-mutated tumor antigen are expressed at high

levels and remain responsive to the P1A antigen when assayed in vitro, it was found that P1A antigen expressed in the thymus resulted in clonal deletion of said specific T-cells Sarma et al note that although said transgenic mice produce an overwhelming majority of T cells that are specific for P1A, said mice are no more resistant to cells expressing P1A than non-transgenic litter mates. Sarma et al concludes that even thought P1A can be a tumor rejection antigen, the effector function of P1A specific CTL is restrained in vivo and that these results have important implications for the strategy of tumor immunotherapy. With regard to the isolation of two T-cells which are specific for the instant antigen presented in the context of HLA-A24, it cannot be determined if this is a reliable indicator that in all patients, with any of the types of cancers listed on page 20, would have a T-cell available after thymic selection which would react with said antigen in the context of HLA-A24 or any other MHC molecule.

The specification does not provided any evidence that any of the vast number of possible potential SEQ ID NO:2 derived T-cell epitopes might be able to be used for cancer therapy. It is concluded based on the references discussed above, that the state of the art with respect to treating cancer patients of administering tumor antigens is unpredictable. The specification does not provide any disclosure that the administration of the claimed polypeptides would generate CTLs which lyse the cells of a tumor and it cannot be predicted based on disclosure of the specification.

Considering the limited guidance, no working examples in the specification, and the unpredictability in the art, it is concluded that undue experimentation is required to use the full scope of the claimed invention. It is noted that law requires that the

disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

Claim 78 is drawn to a kit comprising a nucleic probe. However, the intended use for the probe is to detect a SIMP polypeptide. Neither the specification nor any art of record teaches a nucleic acid probe could detect a SIMP polypeptide. Amending the intended use as "for determining the amount of a nucleic acid encoding a SIMP polypeptide" would obviate this rejection.

Claims 1-6, 8, 10-17, 48-50, 52, 68, 69, 78, 79, and 81-83 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the **written description requirement**. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The applicable standard for the written description requirement can be found: MPEP 2163; University of California v. Eli Lilly, 43 USPQ2d 1398 at 1407; PTO Written Description Guidelines; Enzo Biochem Inc. v. Gen-Prove Inc., 63 USPQ2d 1609; Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111; and University of Rochester v. G.D. Searle & Co., 69 USPQ2d 1886 (CA FC 2004).

Claims 1-6, 8, 10-17, 48-52, 68, 69, 78, 79, and 81-83 are interpreted as drawn to genus of human nucleic acid molecules with various of degrees of differences in terms of structures, i.e. "homologs", "paralogs", 63% to 97 % sequence identity to either

human nucleic acid (SEQ ID NO:1), or a fruit fly nucleic acid (SEQ ID NO 7), or comprising a partial sequence.

To provide adequate written description and evidence of possession of a claimed genus, the specification must provide sufficient distinguishing identifying characteristics of the genus. The factors to be considered include disclosure of complete or partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation, methods of making the claimed product, or any combination thereof.

As for claim 1-3, drawn to a genus of isolated nucleic acid molecules that are expressed ubiquitously in human cells, but also overexpressed in tumor cells, the neither the claims nor the specification teach any structure of such nucleic acid, let alone genus. The specification does not even establish that instant SEQ ID NO:1 nucleic acid is expressed ubiquitously in human cells, but also overexpressed in cancers. It is noted that law requires that the disclosure of an application shall inform those skilled in the art how to make the alleged discovery, not how to screen it for themselves.

As for claims 4 and 5, drawn to a genus of homologs of SEQ ID NO:6, or paralogs of SEQ ID NO NO:12, claims 4,and 5 do not have a complete structure of a single species, let alone a representative number of species that belong to the claimed genus of homologs or paralogs, nor do the claims have a partial structure, physical and/or chemical properties, functional characteristics, structure/function correlation,

methods of making the claimed product, or any combination thereof of the claimed of paralogs of homologs.

As for claims 6, 8, 11, 12, 48, 50, and 69, the only factor present in the claims is a partial structure in the form of percent sequence identity for claim 6, 8, and 12, and "hybridizes" to SEQ ID NO:1 or its complementary under the undefined, subject to interpretation of "under high stringency conditions" for claims 48, 50, and 69 (note 112/2 rejection above). The partial structure is not coupled with any other sufficiently distinguishable identifying characteristics of the genus. In other words, the partial structure is not coupled with functional characteristics that belong to the genus. Accordingly, in the absence of sufficient recitation of distinguishing identifying characteristics, the specification does not provide adequate written description of the claimed genus.

As for claims 13, 68, and 69, the written description rejection is made because of the transitional phrase "comprising" in line 1 along with "having at least 15 nucleotides" in step c) of claim 13, or "40" in claim 68. The genus encompasses full-length genes and cDNAs (such as differently spliced isoforms of said full-length gene) that are not further described. There is substantial variability among the species of DNAs encompassed within the scope of claim 13.

As for claim 15, and 83, drawn to a nucleic acid encoding " a SIMP polypeptide" the specification at paragraph [0098] defines SIMP, "SIMP nucleic acid: means any nucleic acid (see above) encoding a mammalian polypeptide that has the potential of generating a plurality of protein fragments binding with high affinity to MHC molecules,

and having at least 90%, preferably at least 95% and most preferably 100% identity or homology to the amino acid sequence shown in SEQ. ID. NO: 2 (human) or 4 (mouse). When referring to a human SIMP nucleic acid, the nucleic acid encoding SEQ. ID. NO: 2 is more particularly concerned. SIMP protein or SIMP polypeptide: means a polypeptide, or fragment thereof, encoded by a SIMP nucleic acid as described above." Therefore, the "a SIMP polypeptide" is another form of partial structures that encompasses a structure having at least 90% identity. The partial structure is not coupled with any other sufficiently distinguishable identifying characteristics of the genus such as functional characteristics or other physical characteristics.

As for claims 49, and 52, there is no structure associated "human SIMP'" in claim 49, or "a human SIMP antisense nucleic acid" given the conflicting definition of "antisense" in the instant specification. Note the definition of "antisense" in instant claim 48 is nucleic acid hybridizes both the sense and antisense strands, while the ordinary meaning of antisense is a complementary sequence to a segment of genetic material (as mRNA) and serving to inhibit gene function according to Merriam-Webster Online dictionary downloaded on 12/27/04 from url>>http://www.m-w.com.

Vas-Cath Inc. v. Mahurkar, 19USPQ2d 1111, clearly states "applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention. The invention is, for purposes of the 'written description' inquiry, *whatever is now claimed.*" (See page 1117.) The specification does not "clearly allow persons of ordinary skill in the art to recognize that [he or she] invented what is claimed." (See Vas-Cath at page 1116). As discussed

above, the skilled artisan cannot envision the detailed chemical structure of the encompassed genus of nucleic acid molecules, given that the specification has only described SEQ ID NO: 1Therefore, only isolated nucleic acid comprising SEQ ID NO:1, but not the full breadth of the claim meets the written description provision of 35 U.S.C. §112, first paragraph.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 48-51, 68 are rejected under 35 USC 101 because the claimed invention is directed to non-statutory subject matter.

Claims 48-51, and 68 as written, do not sufficiently distinguish over nucleic acids, as they exist naturally because the claims do not particularly point out any non-naturally occurring differences between the claimed products and the naturally occurring products, especially given the disclosure at paragraph [0088], and [0072] of the specification. The specification at paragraph at paragraph [0088] defines "Antisense" to be "nucleic acids, is meant a nucleic acid sequence, regardless of length, that is complementary to the coding strand of a gene." The specification at paragraph [0072] discloses "According to another aspect, the invention features a nucleotide probe comprising a sequence of at least 15 sequential nucleotides of SEQ ID NO: 1 or of a sequence complementary to SEQ ID NO:1." Thus, "a nucleotide probe" and "antisense" could encompass the naturally occurring products that are considered non-statutory

subject matt. The specification does not distinguish "a nucleotide probe" or "antisense" from a naturally occurring product.

In the absence of the hand of man, the naturally occurring products are considered non-statutory subject matter. *See Diamond v. Chakrabarty*, 447 U.S. 303, 206 USPQ 193 (1980). The claims should be amended to indicate the hand of the inventor, e.g., by insertion of "Isolated" or "Purified". See MPEP 2105.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 1-5, 10-17, 48-52, 68, 69, 78, 79, and 81-83 are rejected under 35 U.S.C. 102(b) as being anticipated by WO 98/25962 (18 June 1998).

Claims 1-5, 10-17, 48-52, 68, 69, 78, 79, and 81-83 are interpreted as drawn to an isolated human nucleic acid molecule comprising a sequence complementary to a nucleic acid encoding instant SEQ ID NO:2 (claims 11, and 12), or an isolated human nucleic acid comprising a polynucleotide having at least 15 nucleotides of SEQ ID NO:1, hybridizes to complementary of SEQ ID NO:1 (claims 14, 48-52, 68, 69, 78), wherein the nucleic acid encoding a protein having the potential of generating a plurality of protein fragments binding to high affinity to a human HLA molecule, is expressed ubiquitously in human cells (claim 1), overexpressed in proliferative cells (claim 2), said proliferative cell is tumor cells (claim 3), said nucleic acid being a homolog of the

specified yeast counter part (in claim 4), or paralog of the specified human protein (claim 5), a cDNA (claim 17), wherein "kit" (claim 78), a vector (claims 81, and 82) or a transformed cell (claim 79) comprising the nucleic acid are claimed, and wherein a method of producing a human SIMP polypeptide in claim 83 is claimed.

WO 98/25962 (18 June 1998) at page 79-81, claim 35 teaches SEQ ID NO: 18, which encodes instant SEQ ID NO: 2 protein from the amino acid #504-826 (note attached Exhibit A), and nucleic acid capable of hybridizing to various fragments of SEQ ID NO: 18, how to use the fragments of disclosed human cDNA in DNA sequencing and hybridization analysis at page 29, as T-cell epitopes at pages 39-44, various reagents including reaction buffers for detection at page 32, how to make the protein using the expression vector comprising the disclosed cDNA at page 34-35.

As for claims 15, 16, and 83, claims 15, and 16 as construed defines" a fragment of SEQ ID NO:2" to be "a human SIMP polypeptide."

As for the preamble antisense in claims 48-52, the specification at paragraph [0088] defines "Antisense" to be "nucleic acids, is meant a nucleic acid sequence, regardless of length, that is complementary to the coding strand of a gene." Therefore, the instant claims 48-52 reads on the complementary of SEQ ID NO:18.

WO 98/25962 does not disclose an expression data, or whether the nucleic acid is paralog or homolog of the specified proteins in the instant claim 3, and 4. However, given 100 % match to C-terminal 322 amino acids of instant SEQ ID NO:2 (note the attached sequence alignment, Exhibit A), especially the nucleic acid encoding the SIMP peptide, with a high affinity binding motif for A-0201 HLA molecule i.e. "LMLLMMFAV"

and other sequences (note Table 1 of the instant specification), it appears that the protein encoded by SEQ ID NO:18 of WO 98/25962 inherently has the characteristics specified in instant claims 1-5. The Office does not have the facilities and resources to provide the factual evidence needed in order to establish that the isolated human nucleic acid molecule of the prior art does not possess the same material, structural and functional characteristics of the instantly claimed nucleic acid molecule. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed nucleic acid molecule is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Furthermore, the preamble recitation of antisense (in claims 48-50), pharmaceutical composition (in clam 52), a nucleotide probe in claim 68 is merely suggestive of an intended use and is not given patentable weight for purposes of comparing the claims with the prior art. The claims read on an isolated nucleic acid *per se*.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D. whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey C Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D.
Examiner
Art Unit 1642

MISOOK YU
PATENT EXAMINER

MISOOK YU
PATENT EXAMINER

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Db          2 TTCGCCGTCATCCGCTTCGAAAGCATCATCCACGAGTTCGACCCGTGGTTTAACTATAGA 61

Qy        110 SerThrHisHisLeuAlaSerHisGlyPheTyrGluPheLeuAsnTrpPheAspGluArg 129

Db         62 TCAACACATCATCTTGCATCTCATGGGTTCTATGAATTTTTAAATTGGTTTGATGAAAGA 121

Qy        130 AlaTrpTyrProLeuGlyArgIleValGlyGlyThrValTyrProGlyLeuMetIleThr 149

Db        122 GCATGGTATCCACTAGGAAGAATAGTAGGTGGTACTGTTTACCCAGGGTTGATGATAACC 181

Qy        150 AlaGlyLeuIleHisTrpIleLeuAsnThrLeuAsnIleThrValHisIleArgAspVal 169

Db        182 GCTGGCCTTATTCATTGGATTTTAAATACATTGAACATAACTGTTCACATAAGAGACGTA 241

Qy        170 CysValPheLeuAlaProThrPheSerGlyLeuThrSerIleSerThrPheLeuLeuThr 189

Db        242 TGTGTGTTCCTTGCACCAACTTTTAGCGGCCTTACATCTATATCTACTTTCCTGCTTACA 301

Qy        190 ArgGluLeuTrpAsnGlnGlyAlaGlyLeuLeuAlaAlaCysPheIleAlaIleValPro 209

Db        302 AGAGAACTTTGGAACCAAGGAGCAGGACTTTTAGCTGCTTGTTTTATTGCTATTGTACCA 361

Qy        210 GlyTyrIleSerArgSerValAlaGlySerPheAspAsnGluGlyIleAlaIlePheAla 229

Db        362 GGCTACATATCTCGGTCAGTAGCTGGATCCTTTGATAATGAAGGCATTGCTATTTTTGCA 421

Qy        230 LeuGlnPheThrTyrTyrLeuTrpValLysSerValLysThrGlySerValPheTrpThr 249

Db        422 CTTCAGTTCACATACTATTTATGGGTAAAATCTGTAAAAACTGGGTCAGTTTTTTGGACA 481

Qy        250 MetCysCysCysLeuSerTyrPheTyrMetValSerAlaTrpGlyGlyTyrValPheIle 269

Db        482 ATGTGCTGCTGCTTATCCTATTTCTATATGGTCTCTGCTTGGGGTGGTTATGTATTTATC 541

Qy        270 IleAsnLeuIleProLeuHisValPheValLeuLeuLeuMetGlnArgTyrSerLysArg 289

Db        542 ATCAATCTTATTCCACTGCATGTATTTGTGTTGTTACTGATGCAGAGATACAGCAAAAGA 601

Qy        290 ValTyrIleAlaTyrSerThrPheTyrIleValGlyLeuIleLeuSerMetGlnIlePro 309

Db        602 GTCTACATAGCATATAGCACTTTCTACATTGTGGGTTTAATATTATCAATGCAGATACCT 661

Qy        310 PheValGlyPheGlnProIleArgThrSerGluHisMetAlaAlaAlaGlyValPheAla 329

Db        662 TTTGTGGGATTCCAGCCAATCAGAACAAGTGAACACATGGCAGCTGCAGGTGTCTTTGCA 721

Qy        330 LeuLeuGlnAlaTyrAlaPheLeuGlnTyrLeuArgAspArgLeuThrLysGlnGluPhe 349

Db        722 TTGCTGCAAGCTTATGCTTTCTTGCAGTATCTGAGAGACCGATTAACAAAACAAGAGTTC 781

Qy        350 GlnThrLeuPhePheLeuGlyValSerLeuAlaAlaGlyAlaValPheLeuSerValIle 369

Db        782 CAGACCCTTTTCTTTTTGGGTGTATCACTAGCTGCAGGTGCTGTGTTCCTTAGTGTCATC 841

Qy        370 TyrLeuThrTyrThrGlyTyrIleAlaProTrpSerGlyArgPheTyrSerLeuTrpAsp 389

Db        842 TATTTGACTTATACAGGTTACATTGCACCATGGAGTGGCAGGTTTTATTCATTGTGGGAT 901

Qy        390 ThrGlyTyrAlaLysIleHisIleProIleIleAlaSerValSerGluHisGlnProThr 409

Db        902 ACTGGGTATGCAAAAATACACATTCCAATTATTGCATCAGTGTCTGAGCATCAACCTACG 961

Qy        410 ThrTrpValSerPhePhePheAspLeuHisIleLeuValCysThrPheProAlaGlyLeu 429

Db        962 ACTTGGGTGTCTTTCTTCTTTGATCTACATATTCTTGTATGTACCTTCCCAGCAGGCCTT 1021

Qy        430 TrpPheCysIleLysAsnIleAsnAspGluArg 440

Db       1022 TGGTTCTGCATCAAAAATATCAACGATGAAAGA 1054
```

RESULT 11
AAV44866

```
ID   AAV44866 standard; cDNA; 2546 BP.
XX
AC   AAV44866;
XX
DT   21-OCT-1998  (first entry)
XX
DE   Clone CT585_1 coding sequence.
XX
KW   Secreted protein; nutritional source; cell proliferation activity;
KW   cell differentiation activity; immune stimulant; tissue growth activator;
KW   haematopoiesis regulator; anti-inflammatory; tumour invasion suppressor;
KW   tumour inhibitor; clone CT585_1; ds.
XX
OS   Homo sapiens.
XX
FH   Key             Location/Qualifiers
FT   CDS             112. .972
FT                   /*tag= a
FT
XX
PN   WO9825962-A2.
XX
PD   18-JUN-1998.
XX
PF   12-DEC-1997;   97WO-US023224.
XX
PR   13-DEC-1996;   96US-00766263.
PR   11-DEC-1997;   97US-00989232.
XX
PA   (GEMY ) GENETICS INST INC.
XX
PI   Jacobs K,  Mccoy JM,  Lavallie ER,  Racie LA,  Merberg D,  Treacy M;
PI   Spaulding V,  Agostino MJ;
XX
DR   WPI; 1998-362424/31.
DR   P-PSDB; AAW69247.
XX
PT   New isolated polynucleotides - obtained from human adult testis, human
PT   adult ovary, human adult brain and human adult heart cDNA libraries.
XX
PS   Claim 35; Page 79-81; 108pp; English.
XX
CC   This sequence represents a polynucleotide of the invention, and encodes a
CC   secreted protein. It was isolated from a human adult brain cDNA library,
CC   and is designated clone CT585_1. The DNA sequences and encoded
CC   polypeptides can be used as nutritional sources or supplements, or may
CC   exhibit e.g. cytokine and cell proliferation/differentiation activity,
CC   immune stimulating or suppressing activity, haematopoiesis regulating
CC   activity, receptor/ligand activity, anti-inflammatory activity,
CC   activin/inhibin activity, chemostatic/chemokinetic activity,
CC   cadherin/tumour invasion suppressor activity, tissue growth activity,
CC   tumour inhibition activity or other activities
XX
SQ   Sequence 2546 BP; 837 A; 416 C; 490 G; 803 T; 0 U; 0 Other;
```

Alignment Scores:			
Pred. No.:	0	Length:	2546
Score:	323.00	Matches:	323
Percent Similarity:	100.00%	Conservative:	0
Best Local Similarity:	100.00%	Mismatches:	0
Query Match:	39.10%	Indels:	0
DB:	2	Gaps:	0

US-10-028-384-2 (1-826) x AAV44866 (1-2546)

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Qy        504 LysArgAsnGlnGlyAsnLeuTyrAspLysAlaGlyLysValArgLysHisAlaThrGlu 523

Db          1 AAAAGAAACCAAGGAAATTTGTATGATAAGGCAGGTAAAGTGAGGAAACATGCAACTGAA 60

Qy        524 GlnGluLysThrGluGluGlyLeuGlyProAsnIleLysSerIleValThrMetLeuMet 543

Db         61 CAGGAAAAAACTGAAGAGGGATTAGGCCCTAATATAAAAAGCATTGTCACCATGTTGATG 120

Qy        544 LeuMetLeuLeuMetMetPheAlaValHisCysThrTrpValThrSerAsnAlaTyrSer 563
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Db        121 CTGATGCTATTGATGATGTTTGCTGTCCACTGTACCTGGGTCACAAGCAATGCCTACTCT 180

Qy        564 SerProSerValValLeuAlaSerTyrAsnHisAspGlyThrArgAsnIleLeuAspAsp 583

Db        181 AGTCCAAGTGTAGTCCTGGCCTCATACAATCATGATGGCACCAGGAATATCTTAGATGAT 240

Qy        584 PheArgGluAlaTyrPheTrpLeuArgGlnAsnThrAspGluHisAlaArgValMetSer 603

Db        241 TTTAGAGAAGCTTACTTTTGGCTAAGGCAAAATACAGATGAACATGCACGAGTAATGTCT 300

Qy        604 TrpTrpAspTyrGlyTyrGlnIleAlaGlyMetAlaAsnArgThrThrLeuValAspAsn 623

Db        301 TGGTGGGATTATGGCTATCAGATAGCTGGAATGGCTAATAGAACTACGTTGGTGGATAAT 360

Qy        624 AsnThrTrpAsnAsnSerHisIleAlaLeuValGlyLysAlaMetSerSerAsnGluThr 643

Db        361 AACACCTGGAATAACAGCCACATAGCACTGGTGGGAAAAGCTATGTCTTCTAATGAAACA 420

Qy        644 AlaAlaTyrLysIleMetArgThrLeuAspValAspTyrValLeuValIlePheGlyGly 663

Db        421 GCAGCCTATAAAATCATGAGGACTCTAGATGTAGATTATGTTTTGGTTATTTTTGGAGGG 480

Qy        664 ValIleGlyTyrSerGlyAspAspIleAsnLysPheLeuTrpMetValArgIleAlaGlu 683

Db        481 GTTATTGGCTATTCTGGTGATGATATCAACAAATTTCTCTGGATGGTTAGGATAGCTGAA 540

Qy        684 GlyGluHisProLysAspIleArgGluSerAspTyrPheThrProGlnGlyGluPheArg 703

Db        541 GGAGAACATCCCAAAGACATTCGGGAAAGTGACTATTTTACCCCACAGGGAGAATTCCGT 600

Qy        704 ValAspLysAlaGlySerProThrLeuLeuAsnCysLeuMetTyrLysMetSerTyrTyr 723

Db        601 GTAGACAAAGCAGGATCCCCTACTTTGTTGAATTGCCTTATGTATAAAATGTCATACTAC 660

Qy        724 ArgPheGlyGluMetGlnLeuAspPheArgThrProProGlyPheAspArgThrArgAsn 743

Db        661 AGATTTGGAGAAATGCAGCTGGATTTTCGTACACCCCCAGGTTTTGACCGAACACGTAAT 720

Qy        744 AlaGluIleGlyAsnLysAspIleLysPheLysHisLeuGluGluAlaPheThrSerGlu 763

Db        721 GCTGAGATTGGAAATAAGGACATTAAATTCAAACATTTGGAAGAAGCCTTTACATCAGAA 780

Qy        764 HisTrpLeuValArgIleTyrLysValLysAlaProAspAsnArgGluThrLeuAspHis 783

Db        781 CACTGGCTTGTTAGGATATATAAAGTAAAAGCACCTGATAACAGGGAGACATTAGATCAC 840

Qy        784 LysProArgValThrAsnIlePheProLysGlnLysTyrLeuSerLysLysThrThrLys 803

Db        841 AAACCTCGAGTCACCAACATTTTCCCAAAACAGAAGTATTTGTCAAAGAAGACTACCAAA 900

Qy        804 ArgLysArgGlyTyrIleLysAsnLysLeuValPheLysLysGlyLysLysIleSerLys 823

Db        901 AGGAAGCGTGGCTACATTAAAAATAAGCTGGTTTTTAAGAAAGGCAAGAAAATATCTAAG 960

Qy        824 LysThrVal 826

Db        961 AAGACTGTT 969
```

RESULT 12
AAF98463
ID AAF98463 standard; cDNA; 2546 BP.
XX
AC AAF98463;
XX
DT 07-JUN-2001 (first entry)
XX
DE Human cDNA clone CT585_1 sequence SEQ ID 150.
XX
KW Human; secreted protein; nutrient; cytokine modulator; proliferation;
KW differentiation; immune system modulator; tissue growth; chemotactic;
KW haemostatic; thrombolytic; anti-inflammatory; tumour inhibition; ss;
KW haematopoiesis.
XX
OS Homo sapiens.
XX
PN WO200119988-A1.
XX
PD 22-MAR-2001.
XX
PF 14-SEP-2000; 2000WO-US025135.
XX
PR 17-SEP-1999; 99US-00398829.
XX
PA (GEMY) GENETICS INST INC.
XX
PI Jacobs K, Mccoy JM, Lavallie ER, Collins-Racie LA, Evans C;
PI Merberg D, Treacy M, Bowman MR, Spaulding V, Agostino MJ;
XX
DR WPI; 2001-244801/25.
DR P-PSDB; AAB90727.
XX
PT Isolated nucleic acids encoding polypeptides, useful for modulating e.g.
PT cytokine and cell proliferation/differentiation activity, the immune
PT system and hematopoiesis regulating activity.
XX
PS Disclosure; Page 476-477; 557pp; English.
XX
CC Human cDNA clones represented in AAF98374 - AAF98489 encode secreted
CC proteins AAB90667 - AAB90750. The cDNA clones are isolated from various
CC tissue types, and may be used in the prevention, treatment and diagnosis
CC of diseases associated with inappropriate protein expression. The
CC polypeptides and nucleic acids may be used as nutrients or to modulate
CC cytokine and cell proliferation/differentiation activity and may also be
CC involved in modulation of the immune system. The cDNA sequences,
CC proteins, their agonists and/or antagonists exhibit haematopoiesis
CC regulating activity; tissue growth activity; activin/inhibin activity;
CC chemotactic/chemokinetic activity; haemostatic and thrombolytic activity;
CC receptor/ligand activity; anti-inflammatory activity; haematopoiesis
CC activity; cadherin/tumour suppressor activity; and/or tumour inhibition
CC activity. Included in the invention are probes represented in AAF98490 -
CC AAF98572 which are specific for the cDNA clones encoding the secreted
CC proteins
XX
SQ Sequence 2546 BP; 837 A; 416 C; 490 G; 803 T; 0 U; 0 Other;

Alignment Scores:

Pred. No.:	0	Length:	2546
Score:	323.00	Matches:	323
Percent Similarity:	100.00%	Conservative:	0
Best Local Similarity:	100.00%	Mismatches:	0
Query Match:	39.10%	Indels:	0
DB:	5	Gaps:	0

US-10-028-384-2 (1-826) x AAF98463 (1-2546)

```
Qy        504 LysArgAsnGlnGlyAsnLeuTyrAspLysAlaGlyLysValArgLysHisAlaThrGlu 523

Db          1 AAAAGAAACCAAGGAAATTTGTATGATAAGGCAGGTAAAGTGAGGAAACATGCAACTGAA 60

Qy        524 GlnGluLysThrGluGluGlyLeuGlyProAsnIleLysSerIleValThrMetLeuMet 543

Db         61 CAGGAAAAAACTGAAGAGGGATTAGGCCCTAATATAAAAAGCATTGTCACCATGTTGATG 120

Qy        544 LeuMetLeuLeuMetMetPheAlaValHisCysThrTrpValThrSerAsnAlaTyrSer 563

Db        121 CTGATGCTATTGATGATGTTTGCTGTCCACTGTACCTGGGTCACAAGCAATGCCTACTCT 180

Qy        564 SerProSerValValLeuAlaSerTyrAsnHisAspGlyThrArgAsnIleLeuAspAsp 583

Db        181 AGTCCAAGTGTAGTCCTGGCCTCATACAATCATGATGGCACCAGGAATATCTTAGATGAT 240

Qy        584 PheArgGluAlaTyrPheTrpLeuArgGlnAsnThrAspGluHisAlaArgValMetSer 603

Db        241 TTTAGAGAAGCTTACTTTTGGCTAAGGCAAAATACAGATGAACATGCACGAGTAATGTCT 300
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